National Toxicology Program
Board of Scientific Counselors

December 1, 1998

Doctor,

I have become aware of certain facts with respect to tobacco processing that I believe you should be made aware of. It appears, by default, I have become a leading authority regarding the contamination of tobacco with the well-studied deadly carcinogen, aflatoxin.

I am a medical doctor who has studied this field for twenty years, but only recently have my fears been confirmed. The advent of the Internet has enabled me to amass a formidable amount of evidence linking this toxin to tobacco related disease. I suspect there may be legal and corporate complicity and possibly perjury on the part of the tobacco companies to prevent dissemination of this knowledge. I am also told failure to disclose this knowledge in patent applications also constitutes fraud on the public. ***I believe the tobacco companies are aware of this situation but have concealed it from the public by way of trade secrets to prevent FDA regulation of tobacco.***

My investigation has yielded several results listed below which are accompanied by their respective references:

(1) It has been proved that inhaling aflatoxin-contaminated dust causes cancer in humans. Aflatoxin is a known pulmonary carcinogen.

(2) Dihydrofurans, which are in their essence structurally similar to aflatoxins, have been found to exist in secondhand smoke at levels two to ten times those in primary smoke. When dihydrofurans and dioxins are combusted on tobacco they become chlorinated forming PCDFs and PCDDs.

(3) In my own research, I have demonstrated that aflatoxin, especially when encapsulated in spores (as it is most often found in nature) can survive intact in smoke extracts. Recently discovered documents from the House Commerce Committee reveal RJR and their outside counsel Shook, Hardy, Bacon were aware of research showing the 100% carryover of aflatoxin on contaminated tobacco into the smoke extracts in 1968. Additionally, Dr. Tom Osdene, head of research for Phillip Morris, was aware of this potential contamination of tobacco by mycotoxins in 1965. BAT documents from 1967 revealed the tobacco companies were afraid of FDA regulation similar to the food industry "microbiological contamination" problem, which I interpret as aflatoxin and other mycotoxins. FDA began to regulate aflatoxin on foodstuffs in 1965 or before.

(4) In 1969, scientists for the USDA proved that *Aspergillus flavus* produces aflatoxin on tobacco and published their results in *Applied Microbiology*. Subsequent research on the subject by tobacco companies was done abroad, particularly Germany, and Dr. Osdene had results sent to his home to prevent discovery and by his own admission subsequently destroyed many documents.

(5) Of the fungal species that inhabit flue-cured tobacco, a substantial number are capable aflatoxin producers and their toxicity was verified. Six different studies dating from 1959 to the present show aflatoxin producing fungi are often the species most found on tobacco. Fusarium and Alternaria fungi have also been shown to produce mycotoxins on tobacco, which have been shown to produce emphysema in lab animals. The number of mycotoxins, their quantities, and their eventual fate in primary and ETS are unknown at present. Phillip Morris commissioned a study on this subject in 1994 but the results have not been released to the public.

(6) By securing a U.S. Patent (Number 5,698,599, entitled "Method of Inhibiting Mycotoxin Production," issued December 16, 1997), R.J. Reynolds has effectively acknowledged that tobacco is contaminated with aflatoxin and their patent disclosure describes the toxicology of same. Aflatoxin is heat stable, melting at 269 deg. C. Cigarettes can combust between 50-750 deg. C., and an idling cigarette burns between 50-100 deg. C. A pyrolysis study at Univ. of Kentucky from 1970 showed aflatoxin survived in smoke and smoke extracts when combusted at 200 deg. C., well above the temperature of an idling cigarette producing ETS.

(7) By failing to admit that ammoniation plays a role in remediating aflatoxin contamination, senior tobacco company executives may have committed perjury. Geoffrey C. Bible, under oath before Congress on January 29,1998, and David E. Townsend, the vice president for product development at R.J. Reynolds, and Scott Appleton, the director of scientific and regulatory affairs at Brown and Williamson Tobacco Company, during the Minnesota trial, failed to disclose the crucial role ammoniation plays in decontaminating aflatoxin tainted products. Ammonia was recognized as a viable aflatoxin decontamination technology in 1969 by virtue of a patent assigned to Goldblatt of the U.S Dept. of Agriculture. A 1970 patent describes the use of ammoniated cigarette paper, which reduced the incidence of cancer in mice by 50%. Neither of these patents revealed aflatoxin contaminated tobacco, although recently uncovered industry documents reveal the industry was aware of this fact. Phillip Morris began to ammoniate Marlboro in the early 1970s although to this day they deny aflatoxin is a problem on their products. RJR internal documents explicitly

refute the notion that ammoniation was designed to increase the potency of the nicotine by increasing the free base. Therefore, the decontamination of aflatoxin is the more likely explanation for the use of ammonia. The industry used five million pounds of ammonia in 1984, and ten million pounds annually by 1989. As of 1994 only 40% of RJR's product line was ammoniated. Is the remaining 60% contaminated by any of the dozens of known mycotoxins shown to contaminate agricultural commodities? Are these mycotoxins aerosolized in primary and ETS? FDA should ensure tobacco products are as safe as possible from mycotoxin contamination.

(8) Cigarette smoke is classified as a carcinogen. Benzpyrene is recognized as the primary cancer-causing agent in cigarettes, and aflatoxin is approximately 200 times more carcinogenic than benzpyrene. Dioxins, known human carcinogens, have been found both in primary and ETS by a 1990 Swedish study. Dibenzofurans, essentially structurally similar to aflatoxin, have also been found in ETS. Other smoke studies are equivocal but tar extracts have been shown to highly carcinogenic. Aflatoxins have been found in filters of cigarettes in an Egyptian study. Benzpyrene has been shown to induce the active metabolite of aflatoxin, the epoxide. Benzpyrene is a combustion product and is likely not found on chewing tobacco, yet this product is known to produce oral cancers after several years. Is aflatoxin the culprit? Ammonia has been shown to worsen the effects of the carcinogenic tobacco specific nitrosamines (TSNA's) making both primary and ETS more hazardous.

(9) In cell cultures, both benzpyrene and aflatoxin have been shown to increase titers of the AIDS virus by 500% and 400%, respectively. This means that HIV-infected individuals who inhale *any* tobacco smoke, first or secondhand, may worsen their infection. They will probably increase their chances of developing full-blown AIDS and their infectivity.

(10) Aflatoxin is a profound immunosuppressant, teratogen (causes birth defects), mutagen, and inhibitor of protein synthesis.

(12) Saddam Hussein stockpiled aflatoxin for use against Allied coalition troops or as a terror weapon in the Gulf war. Thus, describing cigarettes and their contamination by aflatoxin as a weapon of mass destruction may not be far off the mark considering the millions of premature deaths caused by their use.

(13) Aflatoxin has been shown to activate *ras* induced lung tumors in mice, the same site shown to play a central role in 30% of human cancers, including 50% of colon, 90% of pancreas, and 25% of lung cancers.

(14) Aflatoxin has been tied to mutations in the gene 17, p53 tumor suppressor at the codon 249 site in liver cancer.

(15) Aflatoxin is widely recognized as a hepatocarcinogen, and some articles suggest the same p 53 tumor-suppressor gene is mutated in 50-60% of lung cancers. It is highly unlikely that this is of no significance.

This in and of itself is highly suggestive of causation or promotion of cancers, but the final proof will lie in finding aflatoxin-DNA adducts at these mutational hotspots on the genome in human lung tissue in smokers. The technology to perform such studies is available. Once neutral researchers are made aware of the link between aflatoxin and tobacco, they will surely perform the requisite tests.

I am preparing a review article for submission to JAMA on this subject, but as you are surely aware, publication will take many months. This is time we cannot spare, given the current politicized nature of the debate over tobacco and the potential Supreme Court case pending with respect to FDA regulation.

Considering the overwhelmingly well documented toxic effects of aflatoxin and the fact that the FDA already monitors this toxin on foods and grains, it is clear that the contamination of tobacco by aflatoxin should be regulated as well. FDA regulates aflatoxin on crops and bars interstate transport of contaminated commodities if the action level of 20 parts per billion is exceeded. For milk this level has been set at 0.5 ppb. ***The documented contamination of tobacco products by aflatoxin is the single most compelling argument for FDA regulation of tobacco products. Dioxin and aflatoxin contamination of tobacco and ETS is a compelling argument for classifying ETS a human carcinogen.***

Surely mycotoxin and aflatoxin-contaminated tobacco poison some of the 200,000-plus Americans who die every year from tobacco-induced cancers. The exact body count will remain unknown until researchers are instructed and enlightened with respect to this situation.

After reviewing the evidence that I have presented, if you are so inclined, you may submit the enclosed supporting documents to several of the appropriate individuals for their opinions with respect to this topic. I hope they will be as impressed by the documents, produced by researchers other than myself, as I was.

As an individual outside the tobacco industry, my ability to assemble and assimilate this body of knowledge suggests to me that surely some individuals inside the industry must be aware of these facts also. Yet these facts are not known to the public, and I believe the industry is less than candid with respect to the multiple roles ammoniation plays in processing tobacco. This is significant due to Mr. Bible's statements under oath before the House Commerce Committee, which by omission did not address

aflatoxin. Mr. Bible is either deliberately uninformed by his research staff or legal counsel or he perjured himself. Perjury and disinformation with respect to this topic has prevented FDA from exercising their legitimate role and led to millions of premature deaths over the last thirty years. ***Failure to invoke appropriate FDA and toxicological regulation, including the mandate of testing for mycotoxins pre and post tobacco processing to ensure adequate decontamination, would leave the consuming public at the mercy of this unscrupulous industry.***

I respectfully suggest ETS be classified as a known human carcinogen. I also urge you to contact your legislators, FDA Associate Director for Tobacco Policy, Mitchell Zeller, and any other appropriate individuals with respect to regulating these harmful compounds

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Respectfully,

Kerry Scott Lane M.D.

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The following journal articles were attached to Kerry S. Lane's comments. Due to copyright infringement laws we cannot display them. We have listed the citations for your information.

National Toxicology Program
Report on Carcinogens Group

Löfroth G, Zebühr Y. 1992. Polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) in mainstream and sidestream cigarette smoke. Bull Environ Contam Toxicol 48:789-794.

Pattee H. 1969. Production of aflatoxins by *Aspergillus flavus* cultured on flue-cured tobacco. Appl Microbiol 18:952-953.

Welty RE, Lucas GB. 1969. Fungi isolated from flue-cured tobacco at time of sale and after storage. Appl Microbiol 17(3):360-365.

Hamilton PB, Lucas GB, Welty RE. 1968. Mouse toxicity of fungi of tobacco. Appl Microbiol 18(4):570-574.

Welty RE, Lucas GB, Fletcher JT, Yang H. 1968. Fungi isolated from tobacco leaves and brown-spot lesions before and after flue-curing. Appl Microbiol 16(9):1309-1313.

El-Maghraby OMO, Abdel-Sater MA. 1993. Mycoflora and antural occurrence of mycotoxins in tobacco from cigarettes in Egypt. Zentralbl Mikrobiol 148:253-264.

Ma X, Gibbons JA, Babish JG. 1991. Benzo[*e*]pyrene pretreatment of immature, female C57BL/6J mice results in increased bioactivation of aflatoxin B_1 in vitro. Toxicology Letters 59:51-58.

Donnelly PJ, Stewart RK, Ali SL, Conlan AA, Reid KR, Petsikas D, Massey TE. 1996. Biotransformation of aflatoxin B_1 in human lung. Carcinogenesis 17(11):2487-2494.

Donnelly PJ, Devereux TR, Foley JF, Maronpot RR, Anderson MW, Massey TE. 1996. Activation of K-*ras* in aflatoxin B_1-induced lung tumors from AC3F1 (A/J□C3H/HeJ) mice. Carcinogenesis 17(8):1735-1740.

Groopman JD, Wang J-S, Scholl P. 1996. Molecular biomarkers for aflatoxins: from adducts to gene mutations to human liver cancer. Can J Physiol Pharmacol 74:203-209.

Dvorackova I, Stora C, Ayraud N. 1981. Evidence for aflatoxin B_1 in two cases of lung cancer in man. J Cancer Res Clin Oncol 100:221-224.

Larsson P, Tjälve H. 1996. Bioactivation of aflatoxin B_1 in the nasal and tracheal mucosa in swine. J Anim Sci 74:1672-1680.

Zalcman G, Trédaniel J, Lechapt E, Lubin R, Soussi T, Hirsch A. 1994. The gene and protein p53 in bronchial carcinoma: biological and clinical aspects. Rev Mal Resp 11:455-472.

Wang TV, Cerutti P. 1979. Formation and removal of aflatoxin B_1-induced DNA lesions in epithelioid human lung cells. Cancer Res 39:5165-5170.

federal register

Tuesday
April 5, 1994

Part II

Department of Labor

Occupational Safety and Health Administration

29 CFR Parts 1910, 1915, 1926, and 1928
Indoor Air Quality; Proposed Rule

TABLE III–7.—PARTICULATE PHASE CONSTITUENTS OF TOBACCO SMOKE AND RELATED HEALTH EFFECTS—Continued

Constituent	Amount in MS	Ratio in SS/MS	Health effects
NNK [4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone]	100–1000 ng	1–4	N/A.[5]
N-nitrosodiethanolamine	20–70 ng	1.2	Probable human carcinogen.[4]
Cadmium	110 ng	7.2	Probable human carcinogen.[4]
Nickel	20–80 ng	13–30	Known human carcinogen.[4]
Zinc	60 ng	6.7	Irritant, nausea, vomiting.[2]
Polonium-210	0.04–0.1 pCi	1.04.0	Known human carcinogen.[4]
Benzoic acid	14–28 µg	0.67–0.95	Irritant.
Lactic acid	63–174 µg	0.5–0.7	Irritant.[3]
Glycolic acid	37–126 µg	0.60.95	Irritant.[2]
Succinic acid	110–140 µg	0.43–0.62	N/A.[5]
PCDD's and PCDF's[6]	1 pg	2	N/A.[5]

[1] NIOSH Pocket Guide to Chemical Hazards. U.S. Department of Health and Human Services. Public Health Services, 1990. Ex. 4–238.
[2] The Merck Index, 10th Edition, Merck & Co., Inc., 1983. Ex. 4–220.
[3] Hazards in the Chemical Laboratory. Ed: L. Bretherick, The Royal Society of Chemistry, 1986. [Ex. 4–137]
[4] EPA: Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders, 1992. [Ex. 4–311]
[5] N/A—Relevant information not available.
[6] PCDDs—Polychlorinated dibenzo-p-dioxins; PCDFs—Polychlorinated dibenzofurans.

MS and SS cigarette smoke are chemically and physically complex mixtures consisting of electrically charged submicron liquid particles at very high concentration consisting of permanent gases, reactive gases, and a large variety of organic chemicals. The composition of the smoke and especially the total quantities of individual constituents delivered are dependent on the conditions of smoke generation [Ex. 4–311].

Nicotine, while found in the particulate phase in MS, is found predominantly in the gas phase in ETS [Ex. 4–100]. The differences in size distribution for MS and SS particles, as well as the different breathing patterns of smokers and nonsmokers, affect deposition of the produced particle contaminants in various regions of the respiratory tract.

There are substantial similarities and some differences between MS and SS emissions from cigarettes [Exs. 3–689D, 4–129, 4–239]. Differences in MS and SS emissions are due to differences in the temperature of the combustion of tobacco, pH, and degree of dilution with the air, which is accompanied by a correspondingly rapid decrease in temperature. SS is generated at a lower temperature (approximately 600°C between puffs versus 800 to 900°C for MS during puffs) and at a higher pH (6.7–7.5 versus 6.0–6.7) than MS. Being slightly more alkaline, SS contains more ammonia, is depleted of acids, contains greater quantities of organic bases, and contains less hydrogen cyanide than MS. Differences in MS and SS are also ascribable to differences in the oxygen concentration (16% in MS versus 2% in SS). SS contaminants are generated in a more reducing environment than those in MS; which will affect the distribution of some compounds. Nitrosamines, for example, are present in greater concentrations in SS than in MS.

Many of the compounds found in MS, which were identified as human carcinogens, are also found in SS emissions [Exs. 3–689D, 4–93, 4–129, 4–239, 4–269] and at emission rates considerably higher than for MS. SS contains ten times more polycyclic aromatic hydrocarbons, aza-arenes and amines as compared with MS [Ex. 4–126]. All of the five known carcinogens, nine probable human carcinogens, and three animal carcinogens are emitted at higher levels in SS than in MS, several by an order of magnitude or more. Several toxic compounds found in MS are also found in SS (carbon monoxide, ammonia, nitrogen oxides, nicotine, acrolein, acetone, etc.), in some cases by an order of magnitude or higher (Tables III–6 and III–7).

SS emissions, quantitatively, show little variability as a function of a number of variables (puff volume, filter versus nonfilter cigarette, and filter ventilation [Exs. 4–1, 4–34, 4–54, 4–128, 4–129, 4–141]. The lack of substantial variability in SS emissions is related to the fact that they are primarily related to the weight of tobacco and paper consumed during the smoldering period, with little influence exerted by cigarette design [Ex. 4–129].

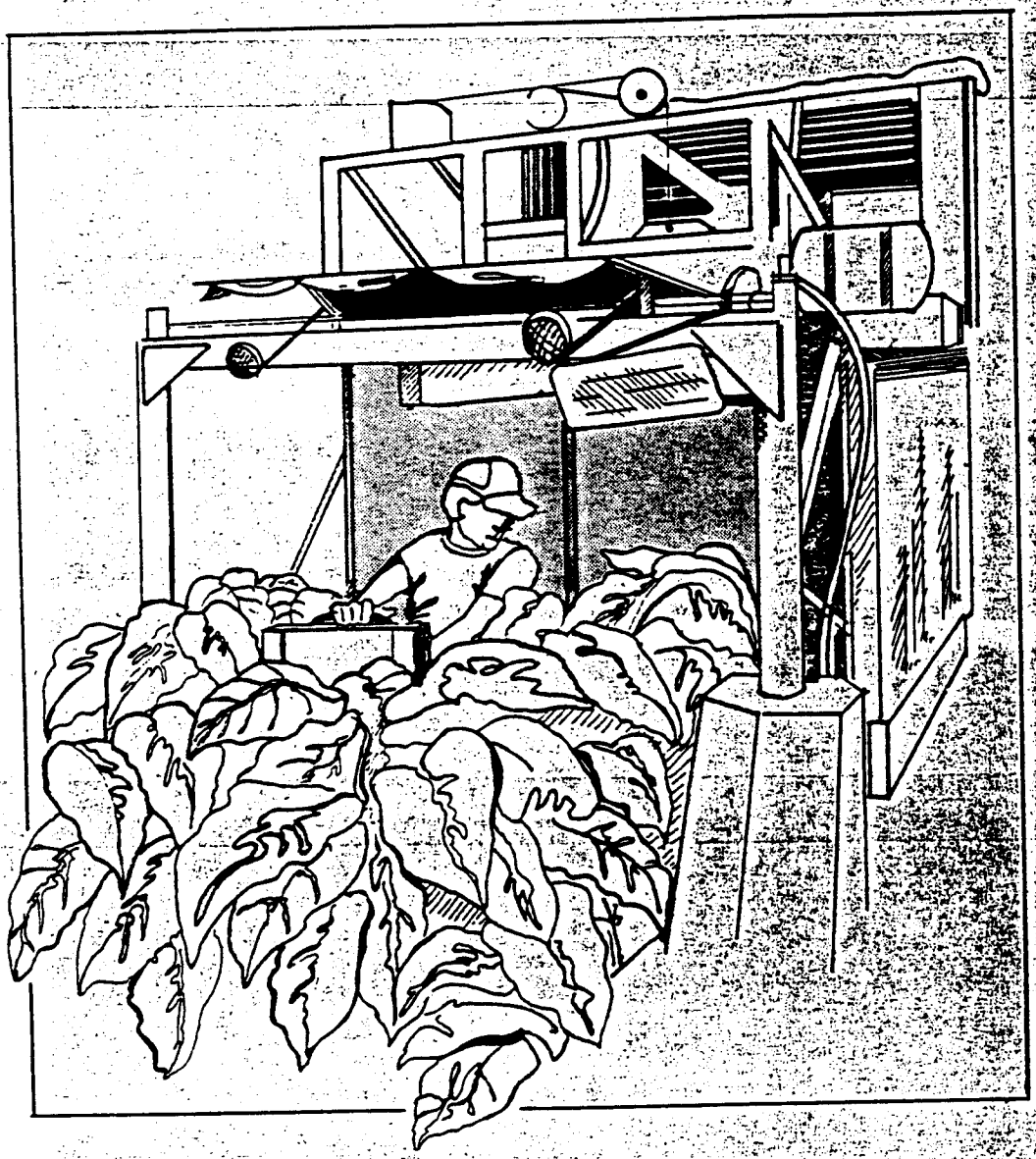
(b) Human Activity Pattern Studies Used to Assess Workplace Exposure. Human activity pattern studies utilize random samples of human activity patterns using questionnaires and time-diary data to provide detailed generalizable data about human behavior. Such studies have been used to assess exposure to ETS. In 1987–1988, the California Air Resources Board sponsored a probability-based cross-sectional sample of 1,579 Californians aged 18 years and older, called the California Activity Pattern Survey (CAPS) [Exs. 4–168, 4–271]. The study was designed to provide information on time spent in various locations, including indoors, outdoors, and in transit, as well as specific microenvironments, such as living rooms, kitchens, automobiles, or buses. The study focused on time spent in activities such as cooking or playing sports, but more specifically targeted activities and environments that had implications for air pollution exposure, such as the presence of smokers, use of cooking equipment or solvents.

In analyzing the data from CAPS, Jenkins et al. [Ex. 4–168] and Robinson et al. [Ex. 4–271] found that time spent at work had a high correlation with exposure to ETS. This association of ETS exposure with work settings remained strong after controlling for the length of the activity episode, and hence was not simply a function of longer time intervals at work. Robinson et al. [Ex. 4-271] also found that men reported higher levels of exposure than women, even after controlling for age, employment status, shorter working hours, etc. This finding suggests that the epidemiological studies of passive smoking and lung cancer, which have focussed on women, may be underestimating the effect of ETS on lung cancer.

Further analysis of the CAP study [Ex. 4–169] verifies the high percentage of nonsmokers who are exposed to ETS while at work. This is indicated when the data are analyzed by employed nonsmoker status. As indicated in Table III–8, 51% of male and 38% of female nonsmokers reported ETS exposure at work. The average duration of this exposure was 313 minutes for males and 350 minutes for females. When the group that reported exposure at the

Flue-Cured

TOBACCO



INFORMATION

1993

NORTH CAROLINA COOPERATIVE EXTENSION SERVICE • NORTH CAROLINA STATE UNIVERSITY

1. FLUE-CURED TOBACCO SITUATION AND OUTLOOK

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An Overview

The 1992 Crop

The October 1 estimate of North Carolina flue-cured tobacco production was just over 587 million pounds, down from about 617 million pounds in 1991. U.S. production was down from about 912 million pounds in 1991, at 893 million pounds. Yields for U.S. flue-cured tobacco were down about 70 pounds per acre, with an October 1 estimate of 2,195 pounds per acre. Decreased yields more than offset increased acreage harvested in 1992. The October 1 estimate of acres harvested was 406,600 acres, up 4,000 acres from 1991.

The flue-cured tobacco markets opened with prices considerably lower than those of the previous year. However, as the season progressed, prices strengthened. It appears that the season average for 1992 will be slightly above that of 1991. As of October 22, 1992, the season average price for all the belts was $1.727 per pound. The season average for 1991 was $1.723. The old and middle belts had the highest season average price per pound at about $1.76, up about 2.5 cents from 1991. The eastern belt 1992 season average was about the same as in 1991, at just over $1.73. The season average prices for the border and Georgia-Florida belts were about $1.70 and $1.68, respectively, both below the 1991 season averages.

The Tobacco Programs

The 1992 effective flue-cured tobacco quota for all the flue-cured-producing states was 899 million pounds, up less than 1 percent from 1991. The 1992 basic quota was 891 million pounds, up about 4 percent from 1991. The 1992 effective quota for North Carolina was 585 million pounds, just under the 1991 effective quota of 587 million pounds. As of October 22, 1992 U.S. flue-cured producers had sold over 892 million pounds or about 99 percent of the effective quota. The 1992 support price for flue-cured tobacco was $1.56 per pound.

Stabilization Situation

The amount of flue-cured tobacco going under loan in 1992 was up about 30 million pounds compared to the 50 million pounds bought by the Flue-Cured Tobacco Cooperative Stabilization Corporation during the 1991 season. Most of the tobacco placed in Stabilization stocks was bought early in the season when sales were slow.

Table 1-3. 1993 Flue-Cured Tobacco Revenue and Cost Estimates (per Acre) for 40-Acres of of Production

Category	Units	Price	Quantity	Value	Your Value
Receipts					
Flue-Cured Tobacco	Lb	$ 1.73	2300	$3979.00	
Operating Inputs:					
Lime Applied	Tons	$31.00	0.405	$ 12.55	
FC Tobacco Seed	Oz	64.00	0.15	9.60	
Custom Fumigation	Sq yd	35.00	0.80	28.00	
12-6-6, Bagged, P.B.	Cwt	10.00	0.40	4.00	
16-0-0, Bagged, P.B.	Cwt	11.82	0.04	0.47	
Blue Mold Cntl.,P.B.	Qt	39.94	0.016	0.64	
Insecticide, P.B.	Lb	8.83	0.016	0.14	
Fld. Blue Mold	Gal	143.78	0.375	53.92	
Nematicide/Insect.	Acre	83.79	1.00	83.79	
Herbicide, Preplant	Gal	29.25	0.187	5.48	
8-8-24, Bagged	Cwt	14.38	5.00	71.90	
16-0-0, Bagged	Cwt	11.82	1.75	20.69	
Insecticide	Lb	8.83	2.00	17.66	
Contact, Suckers	Gal	11.93	4.50	53.69	
Systemic, Suckers	Gal	12.56	1.50	18.84	
Loc. Systemic, Suckers	Gal	50.71	0.50	25.36	
Cover Crop	Acre	12.20	1.2	14.64	
Curing Fuel	Gal	0.88	258.00	227.04	
Electricity	Acre	49.40	1	49.40	
Crop Insurance	$	0.032	2932.00	93.82	
Building Insurance	Acre	80.00	1	80.00	
Selling Charges	$	0.03	3910.00	117.30	
Market Assessment	Lb	0.01	2300.00	23.00	
Leased Quota	Lb	0.00	2300.00	0.00	
Tractor Fuel and Lube	Acre			26.23	
Tractor Repair Cost	Acre			20.04	
Mach. Fuel and Lube	Acre			63.00	
Mach. Repair Cost	Acre			99.45	
Equip. Repair Cost	Acre			40.25	
Total Operating Cost				$1260.90	
Returns To Land, Labor, Capital, Machinery, Overhead, And Management				$2718.10	
Capital Costs					
Annual Oper. Cap.		0.08	449.48	35.96	
Tractor Investment		0.09	212.75	19.15	
Machinery Investment		0.09	1012.78	91.15	
Equipment Investment		0.09	1550.10	139.51	
Total Interest Charge				$ 285.77	
Returns To Land, Labor, Machinery, Overhead, And Management				$2432.33	
Ownership Cost (Depreciation, Taxes, Insurance)					
Tractor	$			18.88	
Machinery	$			115.71	
Barns and Equipment	$			136.56	
Total Ownership Cost				$ 271.15	
Returns To Land, Labor, Overhead, And Management				$2161.18	
Labor Cost:					
Machinery Labor	Hr	$ 6.00	25.91	155.48	
Other Labor	Hr	5.00	121.07	605.35	
Total Labor Cost				$ 760.83	
Returns To Land, Overhead, And Management				$1400.35	

Prepared by G.F. Peedin and D. Smith, Crop Science Extension Specialists, and A. B. Brown, Extension Economist, November, 1992.

Table 3-1. Water Contamination Potential and Mammalian Toxicity of Commonly-Used Tobacco Pesticides

Common Name	Trade Name(s)[a]	Surface Loss Potential[b]	Leaching Potential[b]	LD_{50}[c] Oral	LD_{50}[c] Dermal
acephate	Orthene	Small	Small	866*	10,250*
aldicarb	Temik 15G	Small	Large	2.25*	>2,000*
azinphos-methyl	Guthion	Large	Small	10*	220*
carbaryl	Sevin XLR Plus	Medium	Small	725*	>2,000
carbofuran	Furadan	Small	Large	11	10,200
chioropicrin	Chlor-O-Pic 100	Small	Small	250	----
chlorpyrifos	Lorsban	Large	Small	96-270	2,000
chlomazone	Command	Medium	Large	1,406	>2,000
diazinon	Diazinon	Medium	Large	300-400*	3,600*
dichloropropene	Telone II, Telone C-17[d]	Medium	Large	224	333
disulfoton	Di-Syston	Medium	Small	2-10*	6-20*
endosulfan	Thiodan, Endocide + *	Large	Small	30	359
ethephon	Ethrel	Medium	Total Use	4,400	76,500
ethoprop	Mocap	Medium	Large	46.7	369
fenamiphos	Nemacur	Medium	Medium	5*	80*
ferbam	Carbamate	Medium	Medium	>17,000	----
flumetralin	Prime+	Large	Small	3,100	----
fonofos	Dyfonate	Large	Medium	8-17.5	25*
isopropalin	Paarlan	Large	Very Small	>5,000	----
malathion	Cythion, Malathion	Small	Small	1,000	4,100
maleic hydrazide	Several	Small	Large	3,900	----
mancozeb	Dithane M-45, Manzate 200	Large	Small	11,200	>15,000
maneb	Dithane M-22, Maneb, Manzate	Medium	Small	7,990	----
metalaxyl	Ridomil	Small	Medium	669*	>3,100*
methomyl	Lannate	Small	Medium	17	5,880
methyl parathion	Penncap-M	Medium	Total Use	20	491

Table 3-1. Water Contamination Potential and Mammalian Toxicity of Commonly-Used Tobacco Pesticides (continued)

Common Name	Trade Names(s) [a]	Surface Loss Potential [b]	Leaching Potential [b]	LD_{50} [c] Oral	LD_{50} [c] Dermal
napropamide	Devrinol	Large	Medium	4,640	----
oxamyl	Vydate	Small	Large	5.4*	2,960
parathion	Several	Medium	Small	2	73
pebulate	Tillam	Medium	Medium	921-1,900	4,640
pendimethalin	Prowl	Large	Small	2,679	>2,260
trichlorfon	Dylox, Proxol	Small	Large	250*	>2,100

[a] Most common trade names; others may be in use as well.

[b] Surface loss and leaching potentials by Soil Conservation Service.

[c] LD_{50}: The dose (quantity) of a substance that will be lethal to 50 percent of the organisms in a specific test situation. It is expressed in weight of the chemical (mg) per unit of body weight (kg). The lower the number - the more toxic the chemical. Oral refers to toxicity through ingestion, while dermal refers to toxicity by skin contact. Values are from the Farm Chemicals Handbook '91 and the Herbicide Handbook, 6th Edition.

[d] Telone C-17 also contains chloropicrin.

[e] Endocide + also contains parathion.

* Technical material. Technical material may be more or less toxic than the formulated material.

Table 10-1. Tobacco Disease Losses, 1991-1992

Disease	1991[a] Percent	1991[a] $	1992[a] Percent	1992[a] $	% of Total Disease Loss
Field Losses:					
Granville wilt	1.846	20,326,421	1.252	13,744,553	23.3
Black shank	2.147	23,640,751	1.000	10,974,408	18.6
Mosaic	0.813	8,951,994	0.573	6,287,598	10.6
Root-knot nem.	0.604	6,650,682	0.553	6,071,053	10.3
Brown spot	0.647	7,124,158	0.497	5,455,190	9.2
Target spot	0.320	3,523,540	0.424	4,657,290	7.9
Barn rot	0.288	3,171,186	0.354	3,883,412	6.6
Weather fleck	0.100	1,101,106	0.119	1,308,955	2.2
Soreshin	0.206	2,268,279	0.110	1,203,268	2.0
Tomato spot. wilt	0.080	880,885	0.106	1,168,761	2.0
Hollow stalk	0.052	572,575	0.090	984,653	1.7
Angular leafspot	0.104	1,145,151	0.078	858,931	1.5
Other nematodes	0.036	396,398	0.057	621,514	1.1
South. stem rot	0.058	638,642	0.053	582,525	1.0
Misc. leaf	0.051	561,564	0.052	568,961	1.0
Misc. root dis.	0.019	209,210	0.023	251,314	0.4
Fusarium wilt	0.015	165,166	0.012	134,332	0.2
Etch	0.014	154,155	0.011	122,100	0.2
Ringspot	0.007	77,078	0.011	121,536	0.2
Vein-banding	0.004	44,044	0.007	72,994	0.1
Black root rot	0.005	55,055	0.003	33,263	0.1
Charcoal rot	0.006	66,066	< 0.001	166	< 0.1
Blue mold	0.003	33,033	0.000	0	0.0
Totals	7.425	81,757,139	5.385	59,106,777	100
Plant Bed and Greenhouse Losses:[b]					
Damping-off	0.374	131,390	0.291	117,262	
Anthracnose & Target spot	0.245	86,071	0.171	68,670	

[a] The 1991 ($1,101,106,250) and 1992 ($1,097,586,695) crop values used were the October crop estimates corrected for disease loss.

[b] The 1991 plant bed and greenhouse value was estimated to be $35,131,125, and the 1992 value was $40,267,008.

barn with a faulty burner, a bad thermostat, or a leaking roof. Not only will the quality of the tobacco be lower, but it will cost more to cure with an improperly maintained barn.

There are more than 50,000 bulk barns in North Carolina. Some of these barns are approaching 30 years old, and quite a few are beginning to show their age. A statewide bulk barn energy audit program conducted 10 years ago demonstrated conclusively that the quality of cured tobacco as well as the cost of curing depended heavily on the condition of the barn. There were documented fuel savings as high as 50 percent when poorly maintained barns were thoroughly reconditioned. A bulk curing barn is not so much a structure as a piece of equipment. And, like any piece of equipment, it requires (and deserves) periodic maintenance to keep it in good shape. A good barn maintenance plan should consider the whole barn.

Insulation

Curing fuel is a significant cost of tobacco production. Even a brand new, well-insulated bulk barn uses only about 60 percent the heat value of the fuel to cure the tobacco. The rest of the heat is lost through the walls of the barn by conduction and radiation or through air leaks. Leaky and poorly maintained barns without insulation, on the other hand, may waste 60 percent of the fuel. Many growers do not realize how much fuel their older barns are wasting until they put a new barn down beside their old ones. The difference in fuel use sometimes can be startling.

Most bulk barns are situated on a 4-inch pad of concrete. Some pads are insulated, but most are not. This is unfortunate since test after test has shown that even a small amount of insulation will reduce the amount of fuel used and pay for itself several times over during the life of the barn. It may be too late to do much about an uninsulated pad now, but if you are thinking of putting in a new barn or moving an old one, you might want to consider an inch of foam insulation under the concrete.

Most of the bulk barns made today are insulated. Many of the older ones are not. There is nothing that can reduce the cost of curing like properly installed insulation. There are several ways a bulk barn may be insulated. Growers have used fiberglass batts and foam board with some success. However, experience has shown that the best all-around insulation for a bulk curing barn is sprayed-on polyurethane. In addition to its excellent insulation properties, it will seal cracks and openings. One-half to 3/4 inch of sprayed-on polyurethane insulation is usually sufficient. Doubling the thickness of insulation will not double the saving. **Be careful to keep the insulation off the rails of rack-type barns and other places where it may be rubbed off and mixed with the tobacco.**

Sponged Tobacco

Well-grained, porous, cured tobacco exhibiting a dull grayish brown color is termed "sponged." Sponging is caused by allowing the tobacco to overripen in the field or, more often, by yellowing too long in the barn.

Red or Scorched Tobacco

The incidence of red or "dappled" leaves in cured tobacco tends to be associated with certain varieties and appears to be accentuated by high curing temperatures. Scorched tobacco also has a red color but is not confined to any certain varieties. Any tobacco that has been cured with excessive heat (at a temperature above 170°F) is liable to scorch. The excessive heat caramelizes the sugars in the leaf, giving it an off flavor and an odor suggestive of caramel. Scorched tobacco has lowered water-holding capacity, making it difficult to bring into order.

Vein Darkening

The condition of cured tobacco characterized by a darkening of the leaf along the midrib or large lateral veins is called "vein darkening" or "moisture run-back." It is caused by an interruption to the curing process after the leaf dries but before the stem is dry. This allows some of the stem moisture to seep back into the leaf, causing the discoloration. This condition is common to tobacco stored with swelled stems. Further vein darkening may be stopped by refiring, but there is little that will reverse the process.

Barn Scald

A green tobacco leaf remains alive even after it is put into the barn. Like all living organisms, tobacco respires and produces heat. If the tobacco is packed tightly so the heat cannot be removed, the temperature will increase to the point where the tissue is cooked and killed. If heat is applied too fast, the same effect may result from excessive heat and humidity in the curing barn. Tobacco that is packed too tightly or unevenly in the racks or boxes is subject to barn scald. Be sure the leaf is thoroughly dry in the "tight spots" before raising the temperature beyond 135°F. Tobacco that has been scalded will cure a dark chocolate color and have a disagreeable odor.

Bulk Barn Maintenance

Growers often complain of difficulty in curing their crop. Often, the weather, the variety, the barning labor, or some other factor is blamed. However, there is evidence that much of the problem is the increasingly poor condition of many barns. Top-quality tobacco is not likely to come out of a

soil-borne bacterium that enters the leaf or stem through broken places. This bacterium thrives in warm, wet, dark curing atmospheres. It is believed that sunlight and drying help to keep this disease in check in the field. Therefore, it is recommended that rank, sappy "wet weather" lugs not be harvested (especially by machine) on the first day after a rain. If lower leaves must be harvested wet or immediately after a rain, the following special curing precautions may be needed to prevent the development of soft rot during yellowing.

* Operate the fan with dampers wide open and heat turned off until surface moisture is removed from the leaf. This may take as long as 48 hours.

* If heat must be added to remove surface moisture (when it is near 100 percent relative humidity outside), set the thermostat no more than 5°F higher than the outside temperature and provide the maximum ventilation possible without setting green color in the leaf. **The object is to keep the leaf as dry and cool as practical to prevent the multiplication of the soft rot bacterium.**

* If soft rot occurs despite all precautions, process the tobacco through yellowing and leaf drying (to 135°F) as fast as possible without setting the green color. It will be necessary to use more than the normal amount of ventilation (maintain a wet bulb temperature no greater than 100°F).

Some Common Problems with Cured Tobacco

Bulk barns have numerous advantages over conventional stick barns. However, the likelihood of encountering curing problems is greater with a bulk barn. In particular, bulk barns require a higher level of management in order to ensure a successful cure. Although soft rot is probably the most common problem encountered in curing tobacco, some of the others are described below.

Green Tobacco

Cured tobacco that is green, especially on the upper or "butt" end, results from the failure to break down the chlorophyll completely during curing. Immature tobacco or tobacco that has been subject to an excess of nitrogen or drought conditions often cures with a greenish cast. Mature, ripe tobacco that has had insufficient yellowing during curing will also cure out green. Insufficient yellowing occurs if the leaf is dried too fast.

14. MECHANIZATION

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Bulk Curing

Successful and efficient tobacco curing in bulk barns depends on (1) uniform loading of the racks or boxes with quality tobacco; (2) proper placement of the racks or boxes in the barn; (3) adequate airflow through the tobacco; (4) proper control of the curing conditions; and (5) a well-maintained and energy-efficient curing barn.

Top Quality Comes from Field Ripening

You cannot ripen tobacco in the barn. With a tight bulk barn, you can yellow long enough to get the green out, but the quality is not as good as if the tobacco were field ripened. Characteristics other than color tell the graders and buyers whether or not the leaf was ripe when it was harvested. The use of vigorous varieties, along with modern cultural practices, encourage large root systems, making today's tobacco crops slow to ripen. Further, growers with labor and equipment ready, worried about future uncertainties, are prone to harvest early. Patience and forbearance can be golden. Field-ripened leaf cures quicker, better, with less fuel, and with less probability of soft rot.

Load Barns Right for Top Quality

Improperly loaded bulk barns cannot turn out top-quality leaf. Proper and uniform loading is absolutely necessary with rack barns and even more so with box barns. The density of the tobacco in the racks or boxes may vary from fairly loose to fairly tight, provided each is nearly the same. A barn full of racks or boxes that are not uniformly loaded is almost sure to cure improperly and waste fuel and electrical power. Uniformity is the key to adequate airflow, which is necessary for top-quality cures.

In addition, proper placement of racks or boxes is a must for adequate airflow. A 1/2-inch crack between boxes allows as much as 50 percent of the air to "short circuit" past the tobacco. Racks and boxes should be as close together as possible for maximum leaf ventilation and top-quality curing.

Prevent Soft Rot–Harvest Dry

To prevent "Soft Rot" or "Stem Rot" in first and second primings, *make sure the leaf is dry when harvested.* This is especially important in rank crops or wet seasons and with mechanical harvesting. Soft rot is caused by a

Control

Once tobacco is in storage, it should be checked periodically for signs of insects and new damage. Both pests are active primarily from April through October. During this period, tobacco should be checked every week or two. Pests may also be active during warm spells in the winter months, and tobacco should be checked at these times as well. If tobacco moths are found, tobacco should be treated with *Bacillus thuringiensis* as described above. Simply treating the outside of bundles may help but will probably not control an established infestation. Bundles should be opened and the tobacco treated as loose leaves before restacking. If cigarette beetles are found, the tobacco may be fumigated. Fumigants are very hazardous and must be handled carefully to be effective. Furthermore, regulations make it difficult for farmers to legally carry out fumigation on their own. **Thus, fumigation should be done by a professional.** Remember that fumigation controls only insects that are present; it is not a preventive treatment. If the final curing is left hanging in a bulk barn, heating the barn to 140° or 150°F for 1 to 2 hours will probably kill both pests. The tobacco should be dried at low heat before advancing the temperature above 100°F. Heating well-separated sheets of tobacco might be of some help but would require many hours of heat to raise the temperature adequately deep within the bundle. Further, it may be very difficult to bring sheeted tobacco back into order after heating.

Pesticides must be used carefully to protect against human injury and harm to the environment. Diagnose your pest problem and select the proper pesticide if one is needed. Follow label use directions and obey all federal, state, and local pesticide laws and regulations.

8. Do not treat after topping, except in very unusual cases. Budworms seldom cause significant damage to maturing tobacco unless they are very numerous. The 10 percent threshold should be used only before flowering.
9. Destroy stalks and roots promptly after harvest. This practice reduces the food supply for late-season budworms and greatly decreases the number carrying over into the next season.

Protecting Stored Tobacco

Tobacco stored on the farm is subject to damage by two pests, the tobacco moth and the cigarette beetle. Damage by cigarette beetles resembles the small holes chewed by flea beetles. They also leave behind powdery waste that can give tobacco an unpleasant flavor. Damage by tobacco moths ranges from irregular holes to leaves completely stripped except for major veins. These pests may also reduce the grade of tobacco to NOG as a result of silk webbing, droppings and insects in the tobacco.

Prevention

Control of established infestations is difficult, so prevention is very important. The first step is sanitation. Before tobacco is removed from the curing barn, a clean storage area should be prepared. Clean out and burn all tobacco and refuse from the storage area. Tobacco should not be held even temporarily in an area where trash might harbor insect pests. If the tobacco to be stored is the final harvest, it may be best to leave it hanging in the curing barn. This area is heat sterilized during the curing process, and most bulk barns are relatively tight. Bulk barns may also be a good choice as a storage area for sheeted tobacco but must be clean of tobacco trash if new tobacco is not moved in immediately after curing. Tobacco and storage areas should also be treated with *Bacillus thuringiensis* to help prevent tobacco moth infestation. Apply a fine spray to loose tobacco *as it is being sheeted* or to sticks as they are being stacked. This is an easy job at this point, but it is difficult to open sheets and get good coverage later. Rates for treatment with Dipel are as follows:

Tobacco:	2½ teaspoons Dipel 2X per quart water per 100 pounds of tobacco
Storage area:	6 teaspoons Dipel 2X per 2½ gallons water Use ½ gallon per 1,000 square feet of surface area

Brown & Williamson Collection Index

Tobacco Archive Search Results

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Score: 130
Notes: Unused
Author(s): Geffert, G.
Year: 1968

[Analysis of DDT in tobacco]

Secondary Authors: Grice, H.
Date: December 17,
Type of work: Letter
Document ID: 1317.08
Keywords: PESTICIDES

REGARDING ESTIMATIONS OF RESIDUES OF DDT AND RELATED COMPOUNDS IN REPRESENTATIVE SAMPLES OF 1967 CROP US TOBACCO. IN RESEARCH MANAGER'S VIEW THE FIGURES INDICATE AN UNACCEPTABLY HIGH CONTAMINATION OF THE TOBACCO AND THEY THINK THAT THIS SHOULD BE BROUGHT TO THE ATTENTION OF THE USDA WITH THE REQUEST THAT ACTION IS TAKEN TO ENSURE THAT LEVELS IN FUTURE CROPS ARE LOWER. STATES THAT THERE ARE NO IMPEDIMENTS ON T.D.E. WHICH APPEARS TO BE BECOMING THE MAJOR RESIDUE PROBLEM.

Score: 128
Notes: Unused
Author(s): Research Manager
Year: 1968

[Regarding DDT residues in tobacco]

Secondary Authors: Grice, H.
Date: December 17,
Type of work: Letter
Marginalia
Document ID: 1304.01
Keywords: PESTICIDES, HEALTH, TRC, MEDICAL, HEALTH-CLAIMS

ESTIMATIONS OF RESIDUES OF DDT AND RELATED COMPOUNDS IN REPRESENTATIVE SAMPLES OF 1967 U.S. CROP TOBACCO AND THEY ARE LISTED. IN THE IMPERIAL TOBACCO COMPANY'S VIEW, FIGURES INDICATE UNACCEPTABLY HIGH CONTAMINATION OF THE TOBACCO AND WE THINK THE USDA SHOULD KNOW OF IT WITH THE REQUEST THAT ACTION IS TAKEN TO ENSURE THAT LEVELS IN FUTURE CROPS ARE LOWER.

Aflatoxins and Diseases of Current Unknown Etiology

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INTRODUCTION

The aflatoxins produced by certain strains of Aspergillus and fungi are among the most potent genetically disruptive and acutely toxic substances known to man (1) . The ubiquitous nature of these fungi and their ability to grow on and produce aflatoxin on innumerable organic substrates presents a substantial human health hazard. Aspergillus and Penicillium fungi have been shown to exist and thrive in diverse habitats stretching from the polar ice caps to the tropics. The Aspergillus flavus group is generally recognized as the most ubiquitous and prolific of the aflatoxin producers. Its role is that of a storage fungus that contributes to the deterioration of stored wheat, corn, rice, barley, bran, flour, soybeans and peanuts, among others (2). Investigations from six countries have shown that of a total of 1390 isolates of the A. flavus group, 803, or roughly 60% produced some aflatoxin (3). Maximum aflatoxin yields reported for natural substrates range from 4000 ug/gm (4,000,000 parts per billion) on peanut germ, 894 ug/gn on peanuts and 1511 ug/gm on polished rice (4). Hesseltine's prediction that aflatoxin would eventually be found on many agricultural commodities has proved true. It is likely that aflatoxin will continue to be found in food and feedstuffs, whenever warm and moist weather conditions, faulty or inadequate storage facilities, and human error or ignorance combine to create circumstances favorable for fungal growth.

Chemically, the aflatoxins are highly oxygenated heterocyclic compounds resembling substituted coumarins. The compounds occur in two series, aflatoxin B1 (AFB1) and its derivatives, and aflatoxin G1 (AFG1) and derivatives. A total of 13 naturally occurring derivatives have been structurally identified. The carcinogenicity and acute toxicity of aflatoxins in various biologica1 test systems have been extensively studied. There are wide species differences in susceptibility to acute toxicity although no completely refractory species is known. The oral or parenteral acute LD5O values in experimental animals are generally in the range of 5 -15 mg/kg for AFB1 (5). The liver is the main organ affected by acute toxicity, generally exhibiting centrilobular necrosis, bile duct proliferation, and occasionally, cirrhosis. Aflatoxin contaminated feeding experiments have established that aflatoxin levels of 0.1 mg/kg (ppm) and greater consistently induced primary hepatocarcinoma in rats (6). AFB1 has demonstrable carcinogenic properties at a level of 1 ug/kg (ppb) in the diet (7).

Quantitative estimates of human dietary exposure to aflatoxins have shown a positive correlation between dietary aflatoxin consumption and the estimated liver cancer incidence (8). In Thailand the levels of dietary aflatoxins consumed ranged from 3 - 5 to 222 ng/kg body weight per day (9).

Aflatoxins have been suggested as the etiological agent in the acute disease of children known as Reye's Syndrome or Encephalopathy and Fatty Degeneration of the Viscera (EFDV) in Thailand and Australia (10). Robinson has described a similar lethal acute syndrome in infants in India, describing cirrhotic changes, in infants livers and a host of other symptoms usually resulting in death within several days (11). He suspected the etiological agent was an aflatoxin derivative in the mother's milk, apparently due to ingestion of aflatoxin contaminated foodstuffs. He demonstrated the existence of the acutely toxic aflatoxin metabolite in both the mother's milk and the sick infant's urine.

International epidemiologists generally agree that aflatoxins can be acutely toxic to humans. Chronic lower levels of exposure are thought to be responsible for the increased incidence of primary liver carcinoma in Third world countries. In the essay that follows I have proposed that aflatoxins are an etiologic agent in many diseases that plague Western industrialized societies today. I have also proposed the possible emergence of a previously unreported disease entity associated with the use of an aflatoxin contaminated commodity. The basic premise underlying these proposals is that low levels of aflatoxin exposure can be as debilitating and deadly as the more acute forms of aflatoxicosis. The evidence for some of the proposals is scanty, for all it is circumstantial. What follows are my thoughts along these lines.

AFLATOXINS AND MARIJUANA

THEORY

Moldy marijuana may be capable of causing lung cancer among users who smoke it. It is apparently a common practice among marijuana (MJ) smokers to deliberately promote the growth of mold on MJ to increase the potency and hallucinogenic effects of MJ. Conceivably normally appearing MJ may pose a similar health hazard as fungal invasion could occur on MJ while it is being stored and smuggled into the country. The dark damp holds of "smuggling ships" could provide an ideal environment for the growth of aflatoxin producing fungi.

EVIDENCE

Llewellyn and O 'Rear have shown that MJ can support the production of aflatoxin by A. flavus (12). Using a different strain of A. flavus (American Type Culture Collection # 18166) I have demonstrated the production of aflatoxin on MJ. Two uncontaminated street samples of MJ were moistened and inoculated with a solution containing the aflatoxin producing Aspergillus spores. Prior to inoculation the MJ did not exhibit ultraviolet fluorescence when exposed to UV radiation, a presumptive test for aflatoxin contamination.

After one-week of incubation the specimen exhibited heavy fungal growth, blue UV fluorescence, and semi-quantatative analysis by the Association of Analytical Chemist's method (I3) revealed aflatoxins in approximately 120 ppb. When this sample was smoked through an aqueous-benzene mixture it was found that approximately 100 ppb of aflatoxin was present in the smoke condensate. This is in agreement with earlier experimental data, which suggest that burning could, but does not have to decompose aflatoxin (14). Aflatoxin is a heat stable compound, decomposing at approximately 268 degrees Centigrade (570 F). Llewellyn and 0'Rear found their moldy MJ contained aflatoxin in mean concentrations of 8700 ppb (I2). By comparison, the U.S. Government bans the sale or transfer of corn contaminated with aflatoxin in concentrations greater than 20 ppb, milk when it exceeds 0.5 ppb.

If one assumes that aflatoxin is produced by some moldy MJ and survives the smoking process, what happens to it when it enters the users lungs? Conceivably the aflatoxins and other smoke debris are scavenged and consumed by macrophages. The aflatoxin may be lipid soluble and enter the cell membrane directly or through a membrane transport process. Eventually one might expect the aflatoxin could permute to the DNA of any given cell.

Aflatoxins have been linked to alveolar cell carcinoma in man although the aflatoxins were presumably on inhaled A. flavus spores (15). Legator has shown aflatoxins can inhibit mitosis in human lung embryonal cells at levels of 10 ppb (16). At levels of 100 ppb Legator has demonstrated a 100% increase in the formation of giant cells over controls (16). One could interpret these cell culture changes as pre-anaplastic or anaplastic lesions.

If the critical assumptions in the above theory are met it might only be a matter of time before clinically overt carcinoma of the lung becomes apparent in individuals that smoke moldy MJ.

AFLATOXIN AND TOBACCO

THEORY

Aflatoxin is an etiologic agent in lung cancer related to cigarette smoking. Either through chronic low levels of aflatoxin contamination of tobacco or random "higher levels" of contamination from damaged tobacco, aflatoxin gains entry into the users lungs and disrupt the cells genetic machinery, resulting in anaplastic growth.

EVIDENCE

Much of the evidence for this theory is consonant with the MJ-aflatoxin data presented earlier in this paper.

It is generally accepted that cigarette smokers are at a recognized risk for lung cancer. The precise etiological agent(s) responsible have never been definitively identified. Aflatoxin has been implicated in the causality of human alveolar cell carcinoma. Tissue extracts taken at the time of autopsy revealed the presence of aflatoxins in the lung tissues. Well documented effects of AFB1 on DNA include inhibition of DNA and RNA synthesis, inhibition of protein synthesis and marked alterations of nuclear morphology as observed by EM studies (17). It is thought that aflatoxin acts by alkylating DNA much the same as actinomycin D does. The ability of the aflatoxins to produce carcinogenic, teratogenic, and mutagenic responses place this mycotoxin in a select group of compounds such as alkylating agents which are known to inactivate resting DNA.

What is the evidence that aflatoxin might be a common contaminant of tobacco? Welty and Lucas have studied the fungal microbial flora isolated from flue cured tobacco at the time of sale to cigarette manufacturers and after the tobacco had been stored for several months by conventional methods (18) Analysis of their data showed that of the 21 different fungal strains isolated from tobacco, six strains were known to be genetically capable of aflatoxin production. These six strains of fungus were found on 97%, 84%, 83%, 76%, 97%, and 29% of the total number of leaves of non-damaged marketed flue cured tobacco tested. Culture of 9 mm disc samples taken randomly from the same tobacco leaves yielded the presence of known aflatoxin producing strains on 48%, 12%, 16%, 16%, 26%, and 7% of the respective samples taken. Pattee has demonstrated the production of aflatoxins by A.flavus when cultured on flue cured tobacco (19).

If one assumes that some proportion of these fungal species growing on tobacco do indeed produce aflatoxin one has a reasonable model for the development of lung cancer in humans from the inhalation of aflatoxin contaminated cigarette smoke. When one considers the nature of anaplastic growths in general, i.e., the fact that genetic transformation of only one cell can result in an anaplastic growth so debilitating that death ultimately intervenes, the spectre of low level (10 ppb) contamination of tobacco by aflatoxins becomes quite frightening.

In a similar fashion one might suggest that aflatoxin contaminated tobacco is the etiological agent responsible for the development of oral cancers associated with the use of chewing tobacco. Perhaps further research along these lines is warranted.

AFLATOXINS, AUTOIMMUNE DISEASE AND-BLOOD DYSCRASIAS

THEORY

Aflatoxin may be an etiological agent in autoimmune diseases, gammopathies, lymphomas, and leukemia's. It is conceivable that following ingestion and absorption by the GI tract, circulating aflatoxins may genetically alter the formed elements of the blood. One altered "T" cell of the memory type could yield an entire clone of cells with a mutant immunological response directed towards host tissue. Similarly an altered line of " B " cells could result in a Monoclonal gammopathy with its attendant pathology. Genetic disruption of stem cells in bone marrow could result in lymphomas and leukemias. The imaginative pathologist could envision a host of genetic insults and resultant disease depending on the specific cell type involved and the nature of the hypothesized genetic perturbation.

EVIDENCE

The documented effects of aflatoxin on genetic material provide support for the theory that aflatoxins could be responsible for the development of some autoimmune diseases and blood dyscrasias. Much of the data on aflatoxin effects on DNA has already been cited and will not be repeated here.

DNA invariably plays a vital role in the normal homeostasis of the formed blood elements and the immune surveillance system. Aflatoxin is a well documented permuter of human liver DNA. Would one not expect that aflatoxin is capable of altering any or all DNA, wherever it is found? If aflatoxin does act on the formed elements of the blood to cause an altered immune response leading to autoimmune disease, one might expect an increase in malignancies associated with autoinmune diseases. This has been shown to be the case.

AFLATOXINS AND TERATOGENESIS

THEORY

Aflatoxins are an etiological agent in the causality of some human birth defects.

EVIDENCE

Most birth defects at the present time are of unknown etiology. Aflatoxins have been demonstrated to be teratogenic in hamsters in single IP doses of 4 mg/kg (20). Aflatoxins have been shown to cross the transplacental barrier, a prerequisite for teratogenic action. Intuitively, the well documented genetically disruptive actions of aflatoxins are compatible with their hypothesized role as human teratogens. The sensitivity of rapidly dividing cells to aflatoxins has been the basis for the construction of highly sensitive bioassays for this compound.

Low level contamination of foodstuffs could provide the mode of entry of this toxin into the blood stream, and ultimately, to the developing fetus. The nature of the birth defect engendered by aflatoxin would probably be a function of where in the developing fetus the toxin acted and when the exposure occurred during pregnancy.

CONCLUSION

I have suggested aflatoxins may play an etiological role in a wide variety of human diseases of current unknown etiology. Common to all these disease processes is the involvement of the basic genetic material of the cell, the DNA. As a result of this all the disease processes I have discussed are of an anaplastic, proliferate or dysgenic nature. That these diseases should be linked by this common thread called DNA is not surprising as aflatoxins are among the most genetically disruptive compounds known.

In terms of disease models, I feel the theories I have presented are plausible for the following basic reasons:

1) Aflatoxin is carcinogenic, mutagenic, and teratogenic in addition to its nongenetic acute toxicity.

(2) The storage fungi, which produce aflatoxin, are ubiquitous. Regular contamination of foodstuffs and commodities by aflatoxins in Western society is a documented fact.

2) Chemically and physically aflatoxins are stable compounds, to the point that they can survive combustion in cigarettes.

Establishing a cause and effect relationship for aflatoxin pathogenesis in disease processes has been and will remain difficult for the following reasons:

1) Most likely extremely low concentrations (ppb)) of aflatoxins are involved.

2) The noninfectious nature of aflatoxicoses has hampered researchers looking for an infectious etiologically agent in these disorders.

3) The random and sporadic nature of aflatoxin contamination of commodities has prevented the establishment of consistent etiological patterns in these diseases.

4) The establishment of aflatoxin exposure from a medical history in a clinical hospital setting could be a near impossible task.

5) There is probably an extremely long lag period between aflatoxin exposure and development of clinically overt disease. Current thinking suggests a 10 - 20 year lag period before clinically overt lung cancer appears following the original "anaplastic insult".

6) In acute aflatoxicosis, the aflatoxin can often be demonstrated in the affected tissues. This is likely not to be the case in the diseases I have suggested caused by aflatoxin, as the toxin is more than likely long removed from the diseased tissue by the time clinically overt disease becomes manifest.

7) Anaplastic change and disease could conceivable result from genetic insult to one cell. Identification of the original transformed cell with its aflatoxin altered DNA might be difficult.

8) Unlike viral transformations of cell DNA which generally transform cell surface antigens in an identifiable and reproducible manner, the genetic changes elicited by a chemical such as aflatoxin are probably totally random, nonreproducible and nonidentifiable by todays technology.

9) Animal studies designed to confirm or refute the role of aflatoxins in the aforementioned disease processes may be equivocal for the reasons outlined above.

Conclusive proof of the possible aflatoxin etiology in these disease processes may require the development of techniques and utilization of assays and chemical probes heretofore never regularly used in animal or human studies.

Whether or not aflatoxins are shown to be responsible for the disease entities I have discussed I believe aflatoxins and mycotoxin in general will eventually be shown to be important etiological agents in some human disease processes not now understood. As trace contaminants of food and commodities consumed by man they may assume a stature in the etiology of human disease equal to that of the trace nutrients known as vitamins. Inquisitive scientists and imaginative research will ultimately substantiate or refute this notion.

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21. Whew (Wow, that is)

FOR IMMEDIATE RELEASE

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No Kill Date

United States Patent Application Links Grain Toxins to Tobacco: Physician-Researcher Generates New Support for FDA Regulation of Tobacco

Citing a 1968 article published in a mainstream medical journal, a physician-researcher revealed today that a potent carcinogen, aflatoxin, worsens the carcinogenic effects of tobacco consumption. "Tobacco stored in curing barns may become contaminated with aflatoxin, an extremely potent carcinogen that renders agricultural commodities such as peanuts and grains extremely harmful and unmarketable," stated Kerry S. Lane, M.D., who practices in the Boca Raton-Delray Beach area of Florida. He also noted that the toxin's presence in foodstuffs and the experience of the Food & Drug Administration in dealing with aflatoxin contamination make the FDA the ideal authority for monitoring the presence of aflatoxins in cigarettes, which, after all, are processed from another American agricultural commodity, tobacco.

Aflatoxin is a toxic metabolite produced by the common fungus *Aspergillus*, and aflatoxin contamination is a problem when commodities are stored in damp and warm environments. Last year's corn crop in North Carolina was particularly damaged by aflatoxin contamination.

Aflatoxin endangers human health to such a degree that the Food & Drug Administration currently bans the sale and transport of corn and peanuts when the level of aflatoxin contamination exceeds 20 parts per billion (ppb). When levels reach 0.5 parts per billion in milk, it is removed from commerce.

Aflatoxin was one of the agents stockpiled by Saddam Hussein in his arsenal of chemical weapons. [See a study by Anthony H. Cordesman, co-director of the Middle East Program at the Center for Strategic and International Studies, entitled "Weapons of Mass Destruction in Iraq" (November 14, 1996).]

What's more, Dr. Lane related, "Researchers have shown that aflatoxin raises levels of the AIDS virus in the blood 400%, and benzpyrene raises them 500%, when these toxins are exposed to cells in the laboratory." He noted, "This is especially disconcerting, because benzpyrene is already an acknowledged carcinogenic component of tobacco smoke, and benzpyrene stimulates cells to form the

active metabolite of aflatoxin, the epoxide. Furthermore," he said, "aflatoxin causes mutations in the p 53 tumor-suppressor gene at codon 249 in liver cells, the same site often mutated in lung cancer. It is highly unlikely that this is a coincidence."

As Dr. Lane explained, the danger is that "The level and extent of aflatoxin contamination is not being monitored in tobacco products, because the FDA does not presently have jurisdiction over tobacco." He added, "There is a complete disregard for monitoring the presence of this fungal toxin in tobacco products, and it is one of the most potent carcinogens known." He suggested that because it is generally described as a liver carcinogen in Africa and Southeast Asia, researchers have failed to appreciate its role in tobacco-related carcinogenesis.

Lung cancer is a recognized hazard of cigarette smoking, however, and its connection to aflatoxin seems to have fallen through the cracks. "We have not adequately studied its potential to cause smoking-related cancers," said Lane.

In the early 1990's, Swedish researchers found a class of chemicals known as dibenzofurans, a class that includes aflatoxin, in secondhand smoke, at levels two times higher than in primary smoke. Additionally, R.J. Reynolds obtained a patent in December 1997, for a process to inhibit mycotoxin production in refined agricultural products, including tobacco. (Aflatoxins are a subclass of mycotoxins.)

Dr. Lane recently filed an application for a patent that is designed to remediate the threat of aflatoxin contamination in tobacco products. "I do not know of any patents for processes that specifically remediate aflatoxin contamination in tobacco, even though there are patents on inventions that deal with aflatoxin in other agricultural commodities," Lane reported.

One of the most promising approaches to ridding tobacco of aflatoxin may involve spraying ammonia on the tobacco; this has worked on corn and grains. In his research, Dr. Lane found a patent issued in 1974 on an invention that ammoniated cigarette paper, thus reducing tar-induced skin tumors in experimental mice by 50%. Dr. Lane believes that ammoniation may concurrently lower levels of aflatoxin in cigarette smoke.

"The technology I developed is a significant advance over what is already on the market," Dr. Lane explained. "The invention also provides a means for monitoring levels of aflatoxin, and other toxins, at each step as tobacco products are processed," he said.

"This invention deals with a problem that deserves immediate attention, and I hope the FDA is provided jurisdiction by Congress to devote some resources to assessing the role of mycotoxins in tobacco-related disease," concluded Dr. Lane.

###

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Title
[The p53 gene and protein in bronchial carcinogenesis:from biological to clinical aspects]
Author
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Service de Pneumologie, H^opital Saint-Louis, Paris.
Source
Rev Mal Respir; VOL 11, ISS 5, 1994, P455-72 (REF: 167)
Secondary Source ID
TOXBIB/95/116700;
Abstract
The p53 gene codes for a nuclear phosphoprotein which is capable of modulating the expression of certain genes implicated in the regulation of cell division. The mutation of an allele on the p53 gene with loss of the healthy allele, in different tissues such as ***lung***, larynx, bladder, liver, skin, colon and breast, which may or may not be exposed to chemical or physical carcinogens (tobacco, radon, ultraviolet, ***aflatoxin*** B1), is associated with the occurrence of ***cancer***. Indeed, the mutated p53 protein loses its anti-proliferative properties favouring a de-regulation of cellular multiplication with the accumulation of genetic aberrations. The homozygous deletion of the p53 gene in germ cells in the members of certain family ***cancers*** (Li-Fraumeni syndrome) leads to an increased incidence of ***cancers*** in the child or young adult. The most frequent mutations of the p53 gene end in a stabilisation of the mutated protein with immuno-histochemical nuclear marking of the cells carrying such an alteration. In certain patients this stabilisation of the mutated protein ends in auto-immunisation with anti-p53 serum antibodies. Bronchial ***cancer*** is a ***cancer*** of which the mutations of p53 are the most frequent (45-65% of bronchial ***cancer***) as result of the mutagenic effect of tobacco smoke. These mutations seem to be associated with a bad prognosis and indeed to chemo-and radiotherapeutic resistance. The early diagnosis of p53 alterations (in dysplastic lesions or tumours which are only slightly developed) would enable new therapeutic interventions in bronchial ***cancer*** such as gene therapy or radio-immunotherapy to either restore the p53 gene to normality or to eliminate the cells expressing the mutated p53 protein respectively.
Language
Fre

Publication Type
JOURNAL ARTICLE; REVIEW; REVIEW, MULTICASE
CAS Registry Number
0 (Protein p53)

Database: toxline -- Record 4 of 4 selected.

Title
FORMATION AND REMOVAL OF ***AFLATOXIN*** B1-INDUCED DNA LESIONS IN EPITHELIOID HUMAN ***LUNG*** CELLS.
Author

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J Assoc Off Anal Chem 1988 Jul;71(4):685-703

Review of the decontamination of aflatoxins by ammoniation: current status and regulation.

Park DL, Lee LS, Price RL, Pohland AE

Food and Drug Administration, Center for Food Safety and Applied Nutrition, Washington, DC 20204.

Ammoniation of corn, peanuts, cottonseed, and meals to alter the toxic and carcinogenic effects of aflatoxin contamination has been the subject of intense research effort by scientists in various government agencies and universities, both in the United States and abroad. Results of these studies have been well documented over the last 20 years. Engineers have devised workable systems of treatment of whole seeds, kernels, or meals; chemists have identified and characterized products formed from the reaction of aflatoxin B1 with ammonia with and without a meal matrix; biochemists have studied the biological effects of these compounds in model systems; and nutritionists have studied animal responses to rations containing ammoniated or non-ammoniated components. This review describes these studies. Results demonstrate overwhelming support for the efficacy and safety of ammoniation as a practical solution to aflatoxin detoxification in animal feeds.

Publication Types:

- Review
- Review literature

PMID: 3047098, UI: 88330661

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Tenth International Meeting on *N*-Nitroso Compounds, Mycotoxins and Tobacco Smoke: Relevance to Human Cancer

Beijing, China, 2-7 July 1989

SECOND CIRCULAR — APRIL 1988

The International Agency for Research on Cancer, with the patronage of the Chinese Academy of Preventive Medicine and the Academy of Medical Sciences, will be holding this meeting on 2-7 July 1989 in Fragrant Hill (Xiangshan) Hotel at a hill resort about 20 km west of Beijing (conveniently reached by special transport). This circular gives details of the local organization for accommodation and preparation of papers.

Outline of Meeting Programme

(A more detailed programme will be sent in the Third Circular, in December 1988).

2 July	Registration
3 July	Invited presentations on cancers in China, and their etiology (lung, liver, oesophagus, nasopharynx and stomach); exposures to *N*-nitroso compounds, tobacco components and mycotoxins (including formation, occurrence, measurement of exposures *in vivo* and exposure assessment)
4 July	Mechanisms and biological effects (including metabolism, DNA modifications and repair, oxidative damage, oncogene activation, carcinogenicity/mutagenicity, predisposing (genetic) risk factors)
5 July	Full-day excursion
6 July (a.m.)	Development and application of dosimetry methods for determining human exposure
6 July (p.m.)	Workshop: practical aspects for application of dosimetry methods and opportunities for international collaboration (informal discussion on technical aspects of increased international collaboration in this area)
7 July (a.m.)	International collaborative studies on etiology and cancer prevention in China
7 July (p.m.)	Prospects for cancer etiology and prevention

PHILIP MORRIS U. S. A.

INTER-OFFICE CORRESPONDENCE

Richmond, Virginia

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To: R. D. Kinser

Date: January 11, 1990

From: A. H. Warfield

Subject: Trip Report: Tenth International Meeting on N-Nitroso Compounds, Mycotoxins and Tobacco Smoke: Relevance to Human Cancer; IARC, Lyon, France, 25-28 September 1989

This meeting was originally scheduled for 2-7 July 1989 in Beijing, China, but was postponed and reorganized at the headquarters of the International Agency for Research on Cancer (IARC) in Lyon during the last week of September. The Chinese Academy of Preventive Medicine (Beijing, PRC) was one of the co-sponsors, along with the International Programme on Chemical Safety (Geneva, Switzerland), National Cancer Institute (Bethesda, USA), and National Institute of Environmental Health Services (Research Triangle Park, USA).

A large portion of the program was devoted to various aspects of the relationships of nitrosamines in tobacco and smoke to biological systems. In addition, most of the presentations were in the form of posters. A book of abstracts was handed out at the meeting, and all of the papers in their entirety will be published in book form in 1990. In this memo I have attempted to convey current trends in nitrosamine research especially as it relates to tobacco, and summarize some of the more significant papers presented at the meeting. I have included a reference to the number of the paper discussed in the event the reader would like to read the abstract, which I have available.

There were several papers on gastric cancer in relation to N-nitroso compounds. It was stated by D. Forman (O-4) that there is a weak association of gastric cancer with tobacco use. Most of the emphasis on the topic of gastric cancer at the meeting was on endogenous formation of N-nitroso compounds in the stomach (O-4, P-1, P-2, P-3, P-4, P-5, P-7, P-9, P-11, P-12). High doses of ascorbic acid were shown to reduce intragastric formation of NO_2 and N-nitroso compounds (P-2). Papers were presented which indicated that gastric cancer is related to N-nitroso compounds (P-5, P-7, P-9). Bacteria isolated from rat stomachs were shown to efficiently reduce nitrate to nitrite and catalyze nitrosation of morpholine, and bacterially mediated N-nitrosation was shown to be inhibited by ascorbate (P-12, P-76).

W. Lijinsky (NCI, Frederick, MD) presented a poster on determination of O^6- and N^7-methylated or ethylated guanines in DNA from specific organs of rats and hamsters after exposure to various methylating and ethylating carcinogens, mostly N-nitroso compounds (P-37). For N-nitrosoethylmethylamine it was concluded that reactions other than alkylation of the DNA are important in animal tumor production.

A method for measuring endogenous nitrosation/nitration in tissue, blood proteins and urine was presented based on the determination of

3. Again with Mr. Hill's assistance, acquire samples of off-shore tobaccos that have undergone CPA analysis; and submit them (number and identities to be determined) for mycotoxin analysis.

4. With the Leaf Department, determine if, and how, domestic tobacco samples can be analyzed for possible mycotoxin contents, using the same laboratories.

DRAFT

Re: Do cured tobaccos contain mycotoxins? - Strategy and requisite time/expenditure

Objective

Develop a strategy to assess the occurrence and relevance of mycotoxins in cured tobacco and, if occurring, set up a procedure for the routine determination of those mycotoxins considered relevant

Strategy

step 1:

establish a list of mycotoxins generally considered to be relevant for broad screening and

determine their occurrence/concentration extramurally (avoids unnecessary intramural investment in method establishment)

in tobacco samples (various origins, various curing procedures, etc.)

step 2:

select those mycotoxins considered to be relevant for routine determination on the basis of

their occurrence in samples tested in step 1 and/or

their toxicological relevance (based on, e.g., official guidelines for the testing of agricultural products, literature data, in-house toxicity assays)

step 3:

establish analytical methods at INBIFO or other PM facilities applicable to routine analysis

step 4:

routine determinations

Step 1

More than 120 fungi species are known which form mycotoxins. Many of them are carcinogenic, mutagenic, teratogenic, neurotoxic, toxic to liver and kidneys, or cause hemorrhage. First, we prepared a *maximal list* of mycotoxins using general reference books. From this, a *selection list* was prepared containing those mycotoxins which were either mentioned in the fax of 11 Mar.94 or in the El-Maghraby-publication cited in the same fax. An additional data base search for further published literature on mycotoxins in tobacco has not revealed at first look further information. In addition to those mentioned above, several other mycotoxins from the maximal list were added to this selection if noticeably toxic. Please find this selection list attached.

Our selection list was cross-checked with official recommendations for agricultural or food products:

> A working group on contaminants of a Scientific Committee on Food of the Commission of the European Communities has been reflecting since 1993 on the necessity of regulating mycotoxins in agricultural products. Apart from aflatoxins and ochratoxin A, whose carcinogenic potential is already well recognized, research programs to establish toxicological data for risk assessment are considered for zearalenone, trichothecenes, fumonisines, and ergot alkaloids. These mycotoxins classes are included in our selection list.
>
> The U.S. Food and Drug Administration's Division of Contaminants Chemistry is already monitoring aflatoxin levels in various food products. In a 1992 publication, a list of mycotoxins identified as natural contaminants was published all of which are included in our selection list: aflatoxins, citrinin, cyclopiazonic acid, deoxynivalenol, ergot alkaloids, fumonisins, nivalenol, ochratoxin A, patulin, penicillic acid, sterigmatocystin, T-2 toxin, and zearalenone.

A company was found in Germany (Nateo, Hamburg) that seems to be able to perform the analyses of the approx. 50 compounds in the selection list. The price is 360 DEM (approx. 200 USD) per sample and mycotoxin to be determined. This would amount to 10000 USD per tobacco sample. There may be a customs problem in submitting these samples to the above company; however, this could certainly be solved by technical means, e.g., by extracting the tobacco at INBIFO and submitting the extract.

An alternative approach to the screening for mycotoxins would have been a screening for the fungi themselves. However, the microbiological approach is considered more tedious than the analytical chemical approach. In addition, those mycotoxins produced by fungi already killed by, e.g., treating the tobacco, would not be retrieved by the microbiological approach.

DRAFT

Step 2

The determination of the toxic potential of those mycotoxins found in tobacco will have to be mainly based on literature data. In special cases, in-house toxicity assays may be required. The selection for routine analytes will be based on this information. It should additionally include compounds generally considered to be relevant for routine assessment without having been found in the representative samples of step 1, e.g., aflatoxins.

Step 3

The time required to establish the required analytical methods depends on the selection made in step 2. At present, most of the analytical methods are based on thin layer chromatography (TLC). In case we have to establish the methods, we would try to use HPLC instead of TLC. For an estimated number of 15 mycotoxins to be determined, the method establishment is estimated to take 12 months. Since this type of analyses is not in our mainstream business, a high level technician would be involved with 100 % of his capacity.

Step 4

The routine analysis of 15 mycotoxins in an estimated 100 tobacco samples per year would require the full capacity of 1 technician as a rough estimate.

Note

El-Maghraby and coworkers[1] spiked cigarettes with aflatoxins and were able to detect a certain proportion of them in the filter after smoking. This is in contrast to a previous publication of Kaminsky and coworkers[2] who did not find any trace of aflatoxins in the butts, Cambridge filters, gas phase, and ash of spiked cigarettes.

---

[1] El-Maghraby, O.M.O., Abdel-Bater, M.A.
Mycoflora and natural occurrence of mycotoxins in tobacco from cigarettes in Egypt.
Zentralbl. Mikrobiol. 148: 253-264 (1993)

[2] Kaminsky, E.J., Lazarus, J.C., Watson, L.L., Fancher, O.E., Calandra, J.C.
Fate of aflatoxins in cigarette tobacco.
Beiträge zur Tabakforschung 5: 189-192 (1970)

Toxin	Producing Fungi	Biological Effects
ALTERNARIA TOXINS		
alternariol, alternariol monomethyl ether	Alternaria alternata f. sp. lycopersici	
AT toxin	Alternaria alternata	
radicin	Alternaria chrysanthemi	
AFLATOXINS		
aflatoxin B1, B2, G1, G2	Aspergillus flavus Aspergillus parasiticus	LD_{50}: B1: 10 mg/kg BW p.o. rat carcinogen, hepatotoxic
FUSARIUM TOXINS (others than trichothecenes)		
fumonisin B1, B2	Fusarium moniliforme	carcinogen
fusaric acid	Fusarium heterosporium Gibberella fujikuroi	LD_{50}: 230 mg/kg BW p.o. mice
fuserin C	Fusarium spp	carcinogenic dose: 1x 50 mg/kg BW p.o. rat mutagen, carcinogen?, carcinoma of the liver
moniliformin	Fusarium avenaceum Fusarium moniliforme v. subglutinans	LD_{50}: 4.5 mg/kg BW p.o. chicken; LD_{50}: 21-29 mg/kg BW p.o. mouse necrotic
TRICHOTHECENES		
calonectrin	Fusarium nivale	
crotocin	Trichothecium roseum	
deoxynivalenol (syn.: vomicidin)	Fusarium graminearum Fusarium roseum	acute: 0.3 mg/kg feed vomiting suscept: swine, humans?
diacetoxyscirpenol	Fusarium spp	
fusarenon-X	Fusarium spp	
HT-2 toxin	Fusarium sctari Fusarium tricinctum	
neosolaniol	Fusarium spp	
nivalenol	Fusarium nivale	sickness, vomiting

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roridins (diesters of verrucarol)	Myrothecium roridum Myrothecium verrucaria	
scirpene, scirpentriol	Trichothecium roseum	
T-2 toxin	Fusarium tricinctum	nutritional induced toxic alaukia, death, dermal necrosis, hemorrhage
trichodermin	Myrothecium roridum Trichoderma viride	LD_{50}: 500-1000 mg/kg BW s.c. mice
trichothecin	Trichothecium roseum	LD_{50}: ~300 mg/kg BW i.v. mice
verrucarin A to G, J (diesters of verrucarol), verrucarol	Myrothecium roridum Myrothecium verrucaria	LD_{50}: 1.6 mg/kg BW i.v. mice; LD_{50}: 0.54 mg/kg BW i.v. rabbits local irritation and inflammation of the skin

OTHER TOXINS

asteltoxin	Aspergillus stellatus	paralysis of hind-limbs, respiratory impairment
citrinin	Aspergillus niveus Penicillium citrinum	LD_{50}: 110 mg/kg BW p.o. mouse; LD_{50}: 35 mg/kg BW i.p. mice; nephrotoxic, carcinogen suscept.: swine
cyclopiazonic acid	Aspergillus flavus Aspergillus oryzae Penicillium griseofulvum Penicillium verrucosum	LD_{50}: 50 mg/kg BW p.o. mouse hepatotoxic, cancer suscept.: rat, chicken, calves
ergot alkaloids	Claviceps purpurea	
kojic acid	Aspergillus oryzae	mutagen, symptoms of epilepsy
luteoskyrin	Penicillium islandicum	hepatotoxic, cancer
β-nitropropionic acid	Aspergillus oryzae	LD_{50}: 103 mg/kg BW i.v. mouse liver necrosis
ochratoxin A, B, C	Aspergillus melleus Aspergillus ochraceus Aspergillus sulfureus Penicillium viridicatum	LD_{50}: 21 mg/kg BW i.v. rat nephrotoxic, degeneration of the liver, carcinogen, teratogen suscept.: swine, human ?
patulin	Aspergillus clavatus Aspergillus giganteus Aspergillus terreus Penicillium expansum Penicillium urticae	LD_{50}: 35 mg/kg BW p.o. mouse; LD_{50}: 5 mg/kg BW i.p. mice cytotoxin, carcinogen

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penicillic acid	Aspergillus melleus Aspergillus ochraceus Penicillium basmenes Penicillium suaveolens Penicillium thomii	LD_{50}: 35 mg/kg BW p.o. mouse; LD_{50}: 100 mg/kg BW s.c. mice carcinogen
penitrem A	Penicillium crustosum Penicillium palitans	weakness, tremorigenic, convulsant, death, neurotoxin suscept.: cattle, horses, sheep
rubratoxin A, B	Penicillium purpurogenum Penicillium rubrum	LD_{50}: 7 mg/kg BW p.o. rat hemorrhage, hepatotoxic, carcinogen
rugulosin	Penicillium rugulosum	carcinogen, hepatotoxic
satratoxins	Stachybotrys atra	hemorrhage suscept.: horses, humans
sterigmatocystin	Aspergillus spp	LD_{50}: 150 mg/kg BW p.o. mouse liver lesions, cancer
zearalenone, zearalenol	Fusarium graminearum	acute: 0.12 mg/kg feed uterotropic, vulvovaginitis, abortion

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Mycopathologia 1991 Jan;113(1):19-23

Ecotoxicological aspects of aspergilli present in the phylloplane of stored leaves of chewing tobacco (Nicotiana tobaccum).

Varma SK, Verma RA, Jha AK

Post-graduate Centre of Botany, C.M. Science College, L.N. Mithila University, Bihar, India.

Nine different species of Aspergillus were isolated from the phylloplane of stored chewing tobacco (Nicotiana tobaccum) of different ages. The maximum number of species were isolated from 12 and 18 month old leaves. A. ruber, A. ochraceus, A. flavus and A. nidulans were usually associated with older leaves while A. niger, A. fumigatus and A. flavus were isolated from 6 month old leaves. Approximately 18% of Aspergilli were found to be mycotoxigenic. Sterigmatocystin was produced by three different species. A. ochraceus produced patulin and ochratoxin. All aflatoxigenic strains of A. flavus produced aflatoxin B1 but none of the isolates of A. flavus produced aflatoxin G2. The percentage of toxigenic isolates of different species varied considerably.

PMID: 2014047, UI: 91194748

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Re: Coumarin Substitutes/490

Notes : Unused
Author(s) : Rosene, C.
Year : 1984
Secondary Authors : Pepples, E.
Date : June 18,
Type of work : Memo
Document ID: 1320.01
Keywords : ADDITIVES

ABSTRACT

COUMARIN SUBSTITUTES/490 - THERE ARE NO OTHER COMPOUNDS TO REPLACE COUMARIN AS A FLAVOR ON TOBACCO. TWO HOMOLOGS, 6-METHYLCOUMARIN AND DIHYDROCOUMARIN EXHIBIT COUMARIN-LIKE QUALITIES ON TOBACCO BUT NEITHER CAN BE USED AS A DIRECT REPLACEMENT. STATES THAT THEY CURRENTLY USE AN IFF-FORMULATED COUMARIN SUBSTITUTE ON BARCLAY BUT THAT IT DOES NOT MATCH COUMARIN VERY WELL. THE ATTACHMENT, WHICH IS NOT ATTACHED, LISTS DOMESTIC BRANDS CONTAINING VANILLIN, MACE OIL, AND GLYCERIN.

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Wanted to replace Coumarins because Coumarins when combined w/ Aflatox ↑ tumor formation XZ (pg 21.) Mycotoxins (Purchase, ed, tox).